Recognition of microbial viability via TLR-8 is a critical driver of T follicular helper cell differentiation and vaccine responses

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T cell priming & polarization

T–12

Recognition of microbial viability via TLR-8 is a critical driver of T follicular helper cell differentiation and vaccine responses

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Live attenuated vaccines are generally highly efficacious and often superior to inactivated vaccines, yet the underlying mechanisms remain largely unclear. We have previously reported an inherent capacity of antigen presenting cells (APC) to discriminate live from killed bacteria by virtue of a new class of pathogen-associated molecular patterns (PAMPs), so-called *vita*-PAMPs.

Here we identify recognition of microbial viability by human professional APC, such as $CD14^+CD16^-$ monocytes and $CD1c^+$ DC, as a critical stimulus for subsequent T follicular helper (T_{FH}) cell differentiation and vaccine responses. APC distinguish viable from dead bacteria through Toll-like receptor (TLR)-8 dependent detection of bacterial RNA, which is only present in viable bacteria. Selective recognition of viable bacteria is highly conserved across different hosts and bacterial species. Live bacteria, bacterial RNA, or synthetic TLR8 agonists induce a transcriptional program and a specific cytokine profile in human APC conducive to the differentiation of naïve CD4 T cells into fully functional T_{FH} cells. This process requires intact TLR8- and MyD88 signaling and subsequent release of IL-12, and it is not induced upon detection of dead bacteria or other TLR ligands. Accordingly, vaccination with a live attenuated bacterial *Salmonella* vaccine, but not its heat-killed counterpart, induced T_{FH} cell differentiation and robust humoral immune responses in domestic pigs. Finally, we found a hypermorphic *TLR8* polymorphism to be associated with enhanced protective immunity elicited by a live bacterial vaccine against tuberculosis in a large human cohort, linking TLR8 function to protective vaccine responses in humans.

Our study provides detailed mechanistic insights into the often-observed superiority of live attenuated vaccines. We identify TLR8 as a *vita*-PAMP receptor in humans, and a key inducer of T_{FH} cell differentiation and promising target for T_{FH}-skewing adjuvants.

T–13

C5a receptor 1 activation controls Th cell proliferation by pulmonary CD11b+cDC through antigen processing, MHC-II and CD40 expression

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Question: Pulmonary CD11b+conventional dendritic cells (cDC) are the main drivers of CD4+ Th cell activation in allergic asthma. The mechanisms controlling this activation are still elusive. Previously, we found complement activation and a protective role for C5a-mediated C5a receptor 1 activation during allergen sensitization. Here, we determined the impact of locally-produced C5a from pulmonary CD11b+ cDCs on allergen-induced Th cell proliferation.